Amendments to the Specification

Please insert Pages 1 to 2 of the enclosed Sequence Listing after the Abstract and before the Figures in accordance with 37 C.F.R. §1.77(b).

Please amend page 8, lines 12 to 32, to recite:

Additionally, further enhancement of intracellular delivery of a nucleic acid-based drug can be obtained by co-administration of the nucleic acid-based drug/enhancer with an inhibitor of an enzyme that degrades the nucleic acid-based drug, or which expels or effluxes the nucleic acid-based drug from the cell. Example inhibitors of an enzyme that degrades a nucleic acid-based drug include P-glycoprotein inhibitors, such as verapamil, ketaconazole, diltiazem and the like. The nucleic acid-based drug/enhancer combination can also be co-administered with an endosome escape and/or nuclear accumulation agent to further control the location of the nucleic acid-based drug within the cell. Example endosome escape/nuclear accumulation agents include agents having a REDL (SEQ ID NO: 1) endosomal escape motif or a KKKRKA (SEQ ID NO: 2) nuclear localisation motif. Such agents can be conjugated to agents such as farnesyl, AFCME or myristoyl motifs in order to increase lipophilicity. Additionally, the nucleic acid-based drug can be condensed by a DNA condensing agent, such as polylysine, protamine or calcium phosphate, and administered in the presence of an enhancer.

Please amend page 12, line 24, to page 13, line 6, to recite:

Two different FITC labeled antisense oligonucleotides were used: FITC-labeled ELNG05 (5'-GCCCACCGGGTCCACCAT- 3'; complementary to a sequence in the human BCR-Abl mRNA; SEQ ID NO: 3) and FITC-labeled S-PTH-05 (5'-CTAAACTTCCCCTCTTGG- 3', complementary to sequence 153-170 of the human HPT1 receptor mRNA; SEQ ID NO: 4). The enhancers were used at a range of concentrations: C8 from 120mM to 0.12mM and C10 from 13mM to 0.013mM. The uptake of antisense oligonucleotides was also analysed in the absence of enhancers for variable periods of time (30min-60min). Following incubation, cells were washed twice with PBS w/o Ca^{2+},Mg^{2+} and stained with 1μg/ml TexasRed-DHPE (dihexadecanoylglycerophosphethanolamine,

Molecular Probe T-1395) for 15min at 37° C, washed extensively and fixed with paraformaldeyde pH shift (Barcallo, 1995) and mounted for analysis by confocal laser scanning microscopy (CLSM).

Please amend page 17, line 23, to page 18, line 4, to recite:

Caco-2 cells were grown in a 6 well plate until 70-80% confluent. Cells were treated with antisense oligonucleotides S-PTH-01 (5'-GGGCCTGAAGTATCATAG3' ; nucleotides 86-103 of human HPT1 sequence; SEQ ID NO: 5) and S-PTH-02 (5'-CTAAACTTCCCCTCTTGG-3'; nucleotides 153-170 of human HPT1 sequence; SEQ ID NO: 6) at concentrations of 1 or 10μM in 1ml PBS w/o$Ca^{2+}$and Mg^{2+}. Cellular permeation enhancers C8 and C 10 were added to the antisense mix at concentrations of 40mM, 60mM for C8 and 6mM, 10mM for C10. Caco-2 control wells received either antisense or enhancers only. Untreated cells were also included. Cells were incubated for 30 min or 2h (only a few samples were treated for 2h: 10μM antisense plus 40mM C8 or 6mM C10), washed twice with PBS and fresh medium was added. Caco-2 cells were incubated for 36h at37° C.

Please amend page 21, lines 1 to 22, to recite:

Wistar rats in the 190-250 g weight range were fasted for 24 hours prior to study initiation. Animals were anaesthetised with sagetal prior to dose administration and during the dosing procedure were given halothane gas. Injections of drug were made directly into the intestine closed loop 12cm below the pyloris and after four hours the sutures were removed from the intestine. The animals were allowed to recover (food and water available) for 24 or 48 hours. At the termination of the experiment the animals were sacrificed and tissue samples from the intestine (site of injection), liver, kidney, spleen, lung and heart were taken, frozen in dry ice and stored at -80° C. Intra-duodenal injection of antisense oligonucleotide alone, C10 enhancer alone or a mixture of antisense oligonucleotide and enhancer were administrated to two groups of animals (N=4 per group) and the rats were allowed to recover for either 24 hour or 48 hours. Antisense oligonucleotide S-PTH-03 (5'- CCACTATAGCTCCCTGAG-3'; antisense to rat PT-1 receptor, nucleotides 119-136; SEQ ID NO: 7) was administered at

concentration of 10μM, C10 enhancer was used at 5mg or 25mg in combination with antisense and at 25mg for a control group.

Respectfully submitted,

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